

Observations on Asthma

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A review of the present understanding of asthma leads to the following conclusions: an elevated IgE is the principal risk factor in the development of childhood asthma; secondary exposure to a wide range of environmental agents (including indoor bioallergens) accounts for the variations in prevalence; prevalence (defined by a positive answer to the question "Have you ever had doctor-diagnosed asthma?") ranges between 4 and 8% in children. Black children have a slightly higher prevalence than white children in the United States, and in both races boys have a higher prevalence than girls. A high prevalence is found in Puerto Rican children in the United States. Patterns of utilization of health care resources (hospital emergency departments, individual physicians, etc.) are dependent on economic circumstances. Low-income children have higher annual morbidity (days in hospital, days off school, etc.) than higher income children and are more dependent on hospital emergency departments for primary care. Relatively little is known about nonatopic asthma in adults, although virus infections and occupational exposures play some part in its induction. There are some striking examples of asthma attack periodicity, and much may be learned from these. Hospital admissions for asthma have increased in many regions over the past 15 years; it is unlikely that this represents the increased admission of milder cases and hence would indicate that asthma has become more severe. This is likely to be a more sensitive indicator of change than mortality. Associations between indices of health effects and air pollutants indicate that these are probably playing a role in the worsening of asthma. Adverse effects related to SO₂ and NO₂ exposures have been documented, and fine particulate pollution (PM₁₀) is also associated with worsening of asthma. Ozone is an intense respiratory irritant, and, together with acid aerosols, may well be playing a role in the worsening of asthma. It is not known whether any of these agents are affecting prevalence. — *Environ Health Perspect* 103(Suppl 6):243–247 (1995)

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Introduction

The literature on asthma epidemiology is very extensive. Attention has focused on differences in mortality between countries, and in changing mortality rates within individual countries, on differences in mortality between different regions of the same country, and on the question of whether the prevalence of asthma has increased. Patterns of medication and health care practices are believed to have played a role in mortality effects. There have been indications that prevalence may have increased. There is no doubt that, in many countries since 1979, there has been a considerable increase in hospital admission rates for asthma.

The purpose of this brief report is to focus on some unanswered questions and some new information. An excellent review of all aspects of asthma, including epidemiology (1), might be taken as a starting point.

Risk Factors

In 1989, Burrows et al. (2) published the results of a survey of 2657 subjects in a

general population study in Tucson using detailed questionnaire data and serum IgE measurements. They found a striking relationship between the prevalence of asthma and a raised IgE level and concluded that

Regardless of the subjects' status with respect to atopy or their age group, the prevalence of asthma was closely related to the serum IgE level standardised for age and sex ($p < 0.0001$) and no asthma was present in the 177 subjects with the lowest IgE levels for their age and sex.

This data confirmed earlier work on a birth cohort followed in Dunedin in New Zealand (3). IgE levels fall with increasing age; in the 55+ age group, only one-third of the asthmatics had a raised IgE level. Although these studies established beyond doubt the central role of a raised serum IgE as a primary risk factor, the question of risk factors in those that develop asthma later in life remains unresolved.

Many environmental risk factors have been identified; of these, the probable predominant role of house dust mite allergy has been well established. It is generally presumed that contact with environmental agents, including viral infections, is an essential component of the development of asthma. Gregg (4) wrote, "Provided that subjects with bronchial hyperresponsiveness never encounter the environmental agents which are necessary for provoking it,

they will remain free of asthma." However such agents are so common that total avoidance must be a rare circumstance. Nevertheless, Hendrick (5), in a 1989 editorial, noted that when asthma occurs in an identical twin, the concordance rate is only 19%, and he argued from this that environmental factors must be dominant.

Prevalence and Severity

Differences in prevalence are difficult to evaluate because of the difficulty of defining asthma. Halfon and Newachek (6) analyzed data from the 1988 National Health Interview Survey (NHIS) on Child Health in the United States, which involved 47,485 households and 17,110 children. They noted prevalence data for doctor-diagnosed asthma (Table 1).

The prevalence of a persistent wheeze in children is somewhat higher, found in 9.2% of 650 children in Boston (7). If the question is asked about wheezing in respiratory illnesses, the percentage is increased

Table 1. Prevalence of asthma^a

	All incomes, %	Poor, %	Nonpoor, %
All children	4.3	4.8	4.2
White	4.1	4.6	4.1
Black	5.1	5.2	5.1
0–5 years	3.2	4.2	3.1
6–11 years	5.1	5.6	5.1
12–17 years	4.5	4.5	4.6

^aData from Halfon and Newachek (6).

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again. The prevalence of asthma has been carefully documented in the Nordic countries, where considerable effort has gone into standardizing the definitions (8). In Norway, estimates of prevalence have varied between 0.4 and 2.4%; in Sweden, the prevalence estimates are generally higher, varying between 2.0 and 6.8% in different parts of the country and in different age groups; in Finland, estimates vary between 1.0 and 3.0%. The variation within Denmark is large, from a low of 0.9% in one general practice to a high of 10.5% in another. The most recent estimate among Danish schoolchildren was 4.0%. Using standardized questions, the prevalence of asthma in children between 6 months and 11 years of age living in the United States differed according to their ethnic origin (9). The prevalences were Puerto Rican, 11.2%; non-Hispanic whites, 3.3%; non-Hispanic blacks, 5.9%; Mexican-Americans, 2.7%; and Cubans, 5.2%.

Since environmental factors have been shown to be important in relation to exacerbations of asthma in adults in Puerto Rico (10), the higher prevalence might be related to such influences. In a large cohort (574,878) of 19-year-old inductees into the Polish Army, Hertzman (11) noted that in six classes of ascending air pollution as judged by annual SO₂ levels, the prevalence of asthma apparently increased six-fold between those coming from the least polluted and the most polluted regions, but the prevalence was generally low.

From a comparison between two NHANES (National Health and Nutrition Examination Survey) surveys in the United States, the first in 1971 to 1974 and the second in 1986 to 1980, Gergen et al. (12) concluded that the prevalence of asthma in 6- to 11-year-olds had increased from 4.8 to 7.6%. In 1990, Burney et al. (13) compared data from 1973 and 1986 on 15,000 boys and 14,156 girls in Britain and concluded that asthma prevalence had increased by 6.9% in boys and 12.8% in girls over that period. There had also been increases in those who had a persistent wheeze.

Although the evidence of increased prevalence from similar surveys at different intervals of time is generally convincing, the interpretation of different levels in cross-sectional comparisons is obviously difficult. Thus it is hard to imagine that any effect of a community exposure to VOCs on asthma prevalence would be demonstrable by comparing prevalence data, since many other factors are obviously involved.

There is some evidence that there has been no change in the severity of asthma in those admitted to hospitals for the condition. [At the Sick Children's Hospital in Toronto, a tertiary pediatric referral center, 26% of the children who come to the emergency department with acute asthma require hospital admission (14).] If the severity of asthma has not changed in those admitted, then the increased hospital admissions for asthma, which have been very generally noted, must indicate an increase in the severity of the disease.

It is possible that a factor might change the severity of the disease without affecting prevalence; or by increasing prevalence, there may be an increase in the number of relatively severe cases.

Bronchial Hyperresponsiveness

It is known that bronchial hyperresponsiveness is uniformly present in those who have clinical asthma and in those who reply positively to questionnaires about asthma. It is also increased in those with wheezy illnesses. It is also known that normal individuals are found with no such symptoms and with no history of asthma, who are hyperresponsive. In Ontario, Fitzgerald (15) found that in a random cluster of 310 9-year-old Canadian children, mild asthma was present in 8%, moderate asthma in 11%, and severe asthma in 3%. Thirty-five percent of the children were found to have an enhanced methacholine response, and of these, 11% had no history suggestive of asthma. The fraction of hyperresponsive children was about double that found by identical methods in New Zealand.

It seems reasonable to assume that hyperresponsive individuals in the population, even with negative respiratory questionnaire data, might be those at risk

from exposure to environmental agents that increase hyperresponsiveness or induce inflammation in the lung.

Patterns of Health Care and Asthma Periodicity

The NHIS Survey referred to previously (6) provides important data on patterns of health care in relation to asthma. Dividing the population into poor and nonpoor groups, Halfon and Newacheck (6) reported that there were significant differences between them. The data from their paper illustrate the differences (Table 2). Wood et al. in San Antonio (16) also noted the impact of economic circumstances on asthmatic children.

These revealing data show that asthma is a more disabling disease in those without access to regular medical care (and is striking testimony to the importance of such care). It is interesting to compare the data with the documentation provided by McConnochie and his colleagues (17), who reported on lower respiratory tract illness in the first 2 years of life in a suburban pediatric practice in Monroe County, New York. Lower respiratory tract illness was responsible for 23 illness episodes per 100 child-years during the first 2 years of life. In this age group per 100 child-years, asthma only accounted for 1.04 episodes, bronchiolitis accounted for 2.25 episodes, and bronchitis accounted for 13.7. Hospital admissions were required for 5.3% of the asthmatics, 4.9% of those with bronchiolitis, and only 1% of those with bronchitis.

As noted below, epidemics of asthma have been documented in relation to wind-borne agents. The increase in asthma in the autumn in the northern hemisphere has often been attributed to increased respiratory infections. In Vancouver, we found that a peak in emergency visits

Table 2. Patterns of health care in relation to asthma.^a

	All incomes	Poor	Nonpoor
Usual source for sick care			
Doctor's office, %	84.8	64.8	89.7
Hospital clinic, %	5.2	13.0	3.4
Hospital emergency, %	2.9	8.1	1.7
Mean number of doctor visits	4.9	3.2	5.4
One or more hospital admissions			
in past year, %	7.0	10.6	6.0
Hospital days per 1000	781.0	1710.0	515.0
Avg annual bed days	2.8	5.1	2.2
Avg annual school absence days	4.6	8.7	3.8
"Bothered all the time," %	22.1	27.8	20.2
"Limited in usual activities," %	28.6	33.1	26.6

^aData from Halfon and Newacheck (6).

occurred in the third week of September (18). This did not coincide with increased respiratory infections, which generally peaked in December and January. The September asthma peak is unexplained but was not due to a rise in air pollutants; possibly a windborne allergen at that time remains to be identified. We noted that the number of visits was about the same for asthma and for all acute respiratory visits between the age group 0 to 14 and the age group 15 to 60. In the winter months (November to April), acute respiratory visits were strongly associated, in all age groups, with SO_2 levels; in the 61+ age group only, asthma visits were associated with SO_2 . In the summer (May–October) and in the 15 to 60 age group only, both asthma and acute respiratory visits were associated with SO_2 levels. Environmental data on fine particulate pollution were not available, and, as noted below, it is possible that SO_2 was acting as a surrogate for that. It seems likely that important information on asthma worsening can be derived by such studies.

Asthma and Air Pollution

Common air pollutants, almost without exception, present a challenge to asthmatics. Most of the epidemiologic data relate worsening of asthma, as indicated by a variety of indices, to changes in pollutant levels.

Particulate Pollution

Fine particulate pollution (particles less than $10\ \mu\text{m}$ in size; PM_{10}) has been shown to be related to increased emergency visits for asthma (19,20), increased medication use (21), increased symptoms (22), and increased hospital admissions for asthma (10,23,24). It has been shown beyond much doubt that exposure to environmental tobacco smoke (passive smoking) has an adverse effect on asthmatic children (25). This might be due to increased fine particle pollution in the home.

Sulfur Dioxide

Although asthmatics are much more sensitive to SO_2 than nonasthmatics, there are relatively few studies indicating a direct adverse effect at current ambient levels. Goldstein and Weinstein (26) could find no evidence that exacerbations of asthma in New York City were related to SO_2 levels. However, using a novel method of neural network analysis, Moseholm et al. (27) in Denmark recently found that both SO_2 and NO_2 were important determinants of

a decline in evening peak flow measurements. They followed a panel of 28 adult nonatopic asthmatics for 8 months, recording changes in environmental variables and daily medication use. As noted above, we found some associations between SO_2 levels and acute respiratory and asthma emergency visits in Vancouver (18).

As SO_2 levels in most countries have declined considerably over the past 15 years, it is very unlikely that SO_2 could have been responsible for any increase in the severity of the disease.

Photochemical Air Pollution

Ozone is a prime suspect in relation to asthma because it provokes airway inflammation at very low levels (28). Recent work has shown not only that asthma exacerbations are associated with airway inflammation (29–31) but that the lungs of severe long-term asthmatics show evidence of chronic inflammatory change (32). Furthermore, ozone at low levels increases airway responsiveness in both normals and in asthmatics (33,34). In addition, a recent report suggests that ozone exposure may increase the effects of an allergen, probably by increasing lung permeability (35). However, this study was done on very few cases and requires confirmation.

Most epidemiologic studies of hospital admissions have shown a stronger association with pollutants, when all acute respiratory diagnoses are included, rather than with asthma alone; this might be explained by the greater power of the larger numbers. Some differences in classifications of asthma, bronchiolitis, and acute bronchitis must be present in most of these studies. Ozone, aerosol sulphates, and aerosol hydrogen ions have been shown to be associated with increased hospital admissions in northeast North America (Toronto and Buffalo) (24,36). In Atlanta (37) and in New Jersey (38), ozone levels were significantly related to asthma admissions or emergency visits. A complicating factor is that in all these locations increased acid aerosol and sulphate levels often occur as ozone concentrations increase.

Nitrogen Dioxide

Although nitrogen dioxide is apparently capable of increasing airway responsiveness, there is little evidence of any direct effect on asthmatics at ambient levels. However, it has recently been suggested that the epidemics of asthma due to soybean flour only occurred if NO_2 levels had been

significantly raised on the previous days (39); and NO_2 exposure was a significant factor in causing lowering of the peak flow rate in the asthma panel study conducted in Denmark (27). A recent study from Finland also indicated that increased NO_2 levels were associated with a rise in asthma emergency visits (40). These observations indicate that the question of the importance of NO_2 is not yet resolved. Furthermore, the increased prevalence of asthma in Britain (9) has occurred over a period when the general population was exposed to increasing levels of NO_2 (41).

These observations lead to the question of whether these pollutants are responsible for any increase in severity of asthma that may have occurred. This question cannot be specifically answered, but in view of the general increase in the number of people exposed to ozone and NO_2 , and the possibility that modern forms of fine particulate pollution (associated with increasing automobile density) may be particularly dangerous, it is not possible to dismiss their influence.

It has been argued that hospital records were too unreliable to be used in epidemiologic studies. Martinez et al. in Barcelona (42) have validated the use of emergency room data; Delfino et al. (43) in Quebec showed that there was 95% congruence between the diagnosis of asthma on inpatients, as determined by an expert on medical records and as previously communicated by the hospital to the computerized database. These studies indicate that such records are reliable enough for epidemiological purposes.

Other Agents

In Britain, a thunderstorm was associated with an asthma epidemic, possibly due to windborne allergenic particles (44). In Melbourne, Australia, in a similar and remarkable episode, the heavy rain was thought to have released small particles of windborne rye-grass pollen (45). In Barcelona, the unloading of soybeans in the harbor was found to be the cause of outbreaks of severe asthma, and the affected subjects were shown to be sensitive to this material (46). As noted above, it has recently been suggested that elevated levels of NO_2 just prior to the allergen dispersal may have been an important predisposing factor (39). In the American Midwest, exposure to windborne spores of *Alternaria alternata* has been shown to adversely affect asthmatics (47).

Conclusions

Asthma is a complex disease. We know that it is multifactorial, and that in many but not all cases a genetic predisposition followed by an environmental exposure of some sort is a common component. We know very little about nonatopic asthma, and most of what we know has been derived from occupational exposures to such substances as Western red cedar or toluene diisocyanate. Such induced asthmatic states may take a long time to regress once established, and the induction of the asthmatic state is irreversible in some individuals.

We have good reason to be suspicious of the contemporary role of air pollutants, but proof is something else. We have no reason to suppose that our knowledge of agents that might induce or increase hyperresponsiveness is complete. The explanation of the apparent increase in asthma morbidity remains a major challenge. As Barnes remarked in 1987 (48), "Asthma is probably the only common treatable condition whose prevalence and severity is increasing, and there is evidence from several countries that mortality has risen, despite advances in therapy." Burney (49)

observed in 1988 in an editorial titled "Why Study the Epidemiology of Asthma?" that much contemporary attention was being concentrated on mechanistic research in asthma and relatively little on epidemiology. He wrote, "It is as if those wishing to discover the causes of scurvy had concentrated on the pathological processes in the gums of sailors."

Whether or not we wholly subscribe to that sentiment, it seems certain that future epidemiological studies will be needed to expand our understanding of this complex disease.

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